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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,076	06/06/2001	Chen W. Liaw	AREN-0239	6379

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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,076	LIAW ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 77-106 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 77-106 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The indicated allowability of claims of claims 77-106 has been withdrawn.

Claims 77-106 are pending and under consideration by the Examiner.

2. Receipt of applicant's arguments and amendments filed on 9/19/2003 are acknowledged.

3. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 4/13/2004:

(i) the objections to the specification ;

(ii) the objection to claim 87 ;

(iii) the rejection of claims 78-83 and 85-91 under 35 U.S.C. § 112, first paragraph, for the recitation of the phrase "consisting essentially of"; and

(iv) the rejection of claims 78-83, and 85-91 under 35 U.S.C. § 112, second paragraph, for the recitation of the phrase "consisting essentially of".

4. Applicant's arguments filed on 9/19/03 have been fully considered but were persuasive in part. The issues remaining are stated below.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejections-35 U.S.C. 101/112, first paragraph

6. Claims 77-106 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

This rejection is maintained for reasons of record set forth at pages 3-6 of the previous Office action (3/21/03).

The instant invention is drawn to a polynucleotide encoding a protein of amino acid sequence set forth in SEQ ID NO:20, a vector comprising the polynucleotide, and a host cell comprising the vector and a process. Table A, page 8 of the specification discloses that the instant hARE-2 protein has 53% homology to GPR27. The specification fails to disclose whether this homology is random, stretches of homology, or pockets of homology and whether the homology is in conserved or non-conserved areas. Furthermore, Applicants have failed to show the 7 hydrophobic transmembrane domains that are characteristic and highly conserved in GPCRs or alignments of hARE-2 with GPR27.

Table C, page 27 of the specification discloses that hARE-2 is expressed in the left and right cerebellum and in the substantia nigra. Applicants argue that the claimed nucleic acid encodes hARE-2 to be a G-protein coupled receptor (GPCR) selectively expressed in the substantia nigra and that the claims clearly recite such. Applicants have traversed this rejection on the premise that the disclosure of the probable fact that a hARE-2 protein of the instant invention functions as a G protein-coupled receptor protein in the substantia nigra is sufficient for utility. Graph I supplied by Applicants in the arguments of 9/19/2003 was not provided in the application as filed. A protein of unknown function would have utility if it can be employed as an indicator of a diseased state or of the presence of a disorder. The only disclosed function for a protein of the instant invention in the application as filed, however, is as a GPCR protein. It is certain that this protein can be employed to identify compounds which can act as agonist or antagonists of that protein, but this information is without real value because the instant specification does not identify a physiological process such as blood pressure, heart rate, taste, cognition, or sensation of pain which one could expect to influence by the administration of a

compound that has been identified by employing a protein of the instant invention. If a protein of the instant invention was a receptor for a compound, then the protein would have utility in the purification of that compound, but the instant specification, as filed, does not identify any specific compound, which is known to bind to that protein. Applicant is not being required to identify a ligand for that protein, and a physiological process mediated thereby and a disease or disorder for which that protein is a marker. Applicant is only required to identify one substantial, specific and credible utility and, as stated in the previous office action of 3/21/2003, the employment of this protein only as the subject of further research does not satisfy the utility requirement of 35 U.S.C. § 101 because the courts have interpreted this statute as requiring an invention to have "substantial utility" "where specific benefit exists in currently available form".

Applicant asserts that GPCRS disclosed in the background section of the specification, modulate the level of intracellular cAMP (page 12 of the specification, lines 3-7). The specification discloses:

"Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, 5 constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP."

However, the instant specification fails to demonstrate whether there is a reduction or an increase in the level of cAMP to indicate that hARE-2 couples to Gs or Gi. Applicants argue that this data is provided in Applicants arguments of 9/19/2003 demonstrating that hARE-2 constitutively couples to Gi. However, this result is only an assertion but not directly proven by

the experiment the results of which are shown in Graph I. HEK-293 cells were transfected with expression vectors for TSHR and hARE-2 and stimulated with TSH, which binds to TSHR. It is unclear in the experiment what ligand binds to hARE-2. Is the 25% and 30% reduction in the level of intracellular cAMP due to reduction in the transfection efficiencies because of transfection with 2 vectors or is it that hARE-2 is binding the TSH or some other ligand? Was this experiment done with single cells or groups of cells. Could we be looking at a completely unrelated mechanism where hARE-2 activity is via Ca^{2+} as second messenger, which inhibits cAMP release? In any event, the ligand for the claimed hARE-2 protein is unknown, no GTPase assay has been provided, no stimulation of GTPase has been demonstrated in membranes of hARE-2 transfected cells investigating GTPase activity.

An application has to be **complete as filed**, it is not a starting point of further research. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966)*, in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the Court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The Court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where

specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In the absence of a knowledge of the natural ligands or biological significance of the protein in the instant specification as filed, there is no immediately obvious "patentable" use for it.

Applicants argue that at the time of filing, the hARE-2 GPCR, known to be expressed in the substantia nigra had a well-established utility for the prevention of or treatment of motor impairment, including Parkinson's disease. However, in the instant application, compounds that specifically activate or inhibit hARE-2 are not disclosed and neither are diseases associated with hARE-2 dysfunction disclosed.. Furthermore, the specification fails to disclose ligands that bind or activate hARE-2. Each clinical agent, which has been developed by measuring its interaction with a specific GPCR was evaluated against a receptor whose native ligand and physiological function were known, such as the adrenergic receptors, the dopamine receptors and the serotonin receptors There are also numerous GPCRs, such as the odorant receptors, which do not mediate any clinically significant process. More importantly, an artisan knew, before they employed a specific GPCR to identify clinically useful compounds, which physiological process or processes they wished to manipulate and that the receptor protein employed in their assay had an influence of that process. Even if one identifies an agonist or antagonist for a receptor of the instant invention, this information is useless since one has no idea of what clinical effect the administration of that agonist or antagonist to an individual would have.

The following is an excerpt from M.P.E.P. 2138.05:

"CLAIMED INVENTION IS NOT ACTUALLY REDUCED TO PRACTICE UNLESS THERE IS A KNOWN UTILITY

Utility for the invention must be known at the time of the reduction to practice. Wiesner v. Weigert, 212 USPQ 721, 726 (CCPA 1981) (except for plant and design inventions); Azar v. Burns, 188 USPQ 601, 604 (Bd. Pat. Inter. 1975) (a composition and a method cannot be actually reduced to practice unless the composition and the product produced by the method have a practical utility); Ciric v. Flanigen, 185 USPQ 103, 105 - 6 (CCPA 1975) ("when a count does not recite any particular utility, evidence establishing a substantial utility for any purpose is sufficient to prove a reduction to practice"; "the demonstrated similarity of ion exchange and adsorptive properties between the newly discovered zeolites and known crystalline zeolites ... have established utility for the zeolites of the count"); Engelhardt v. Judd, 151 USPQ 732, 735 (CCPA 1966) (When considering an actual reduction to practice as a bar to patentability for claims to compounds, it is sufficient to successfully demonstrate utility of the compounds in animals for somewhat different pharmaceutical purposes than those asserted in the specification for humans.); Rey - Bellet v. Engelhardt,181 USPQ 453, 455 (CCPA 1974) (Two categories of tests on laboratory animals have been considered adequate to show utility and reduction to practice: first, tests carried out to prove utility in humans where there is a satisfactory correlation between humans and animals, and second, tests carried out to prove utility for treating animals.).

A PROBABLE UTILITY MAY NOT BE SUFFICIENT TO ESTABLISH UTILITY

A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." Bindra v. Kelly, 206 USPQ 570, 575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first inter mediate. However, a strong probability of utility is not sufficient to establish practical utility.); Wu v. Jucker, 167 USPQ 467, 472 (Bd. Pat. Inter. 1968) (screening test where there was an indication of possible utility is insufficient to establish practical utility). But see Nelson v. Bowler, 206 USPQ 881, 885 (CCPA 1980) (Relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses. Reasonable correlation between the two is sufficient for an actual reduction to practice.)."

Therefore Applicants have failed to establish a specific and substantial asserted utility or a well established utility for a protein encoded by the nucleic acid of the instant invention at the time the application was filed.

Claims 77-106 are rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
March 14, 2005